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(54) **Title:** EPOTHILONE ANALOGS FOR SITE SPECIFIC DELIVERY IN THE TREATMENT OF PROLIFERATIVE DISEASES

(57) **Abstract:** Conjugates of epothilones and epothilone derivatives (as effectors) with suitable saccharides or saccharide derivatives (as recognition units) are described. Their production is carried out by the recognition units being reacted with suitable linkers, and the compounds that are produced are conjugated to the effectors. The pharmaceutical use of the conjugates for treating proliferative or angiogenesis-associated processes is described.

EPOTHILONE ANALOGS FOR SITE SPECIFIC DELIVERY IN THE TREATMENT OF PROLIFERATIVE DISEASES

In recent decades, a series of highly effective new chemotherapy agents for the therapy of tumors was developed. Despite all of these efforts, the treatment options and the therapeutic window are limited by the high intrinsic toxicity of these pharmaceutical agents.

Only a small portion of the amount of substance administered reaches the tumor (Anderson et al., Clin Pharmacokinet 27, 191-201, 1994; Thorpe et al., Breast Canc Res Treat 36, 237-251, 1995), while the maximum amount of substance is taken up by healthy tissue and thus is responsible for many of the undesirable side effects.

For this reason, the selective release of systemically administered chemotherapy agents at the target site always represents a scientific challenge. More recent developments aim at, for example, detoxifying cytostatic agents by conversion into a prodrug form and cleaving the non-toxic prodrug only when reaching the tumor by tumor-associated enzymes. A validation of this concept could be achieved by Bosslet (Bosslet et al., Canc Res 58, 1195-1201, 1998) in the example of a non-toxic prodrug, based on doxorubicin, which was chemically linked with glucuronic acid. In this case, the finding that an elevated lysosomal ß-D-glucuronidase activity is observed in the necrotic areas of many tumors was used.

On the one hand, the relatively low cytotoxicity of the chemotherapy agent doxorubicin that was used and that required a high dosage of the prodrug proved disadvantageous, and on the other hand, the relatively quick development of resistance against doxorubicin itself proved disadvantageous.

The new structural class of the epothilones and analogs thereof primarily offers a possibility of avoiding these drawbacks. Most natural or synthetically modified compounds from their structural class exert their full antiproliferative activity against the most varied tumor cells that are resistant to other chemotherapy agents. The active strength relative to these cells can be up to 10,000 x greater, compared to chemotherapy agents that are used in clinical practice, such as, for example, taxol, doxorubicin, cis-platinum or camptothecin.

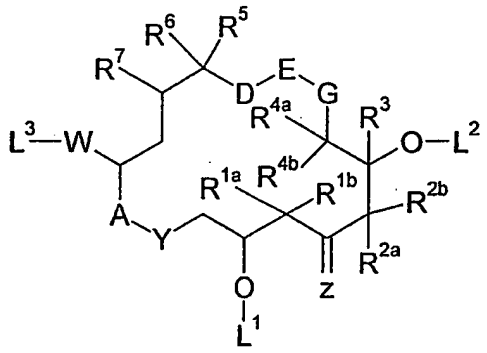
Within the scope of this invention, surprisingly enough, a possibility has now been found to link the chemically very sensitive highly-functionalized active ingredient class of the epothilones and analogs thereof with a recognition unit that contains a saccharide or a saccharide derivative via different linkers to various positions of the active ingredient.

The object of this invention is thus based on, i.a.,

1. Finding a method to link highly active active ingredients from the structural class of the epothilones and epothilone derivatives with suitable recognition units via linkers, whereby the resulting conjugates are adequately stable both chemically and metabolically for a development of pharmaceutical agents and are superior to the underlying epothilone or epothilone derivatives with respect to their therapeutic range, their selectivity of action and/or undesirable toxic side effects and/or their active strength;
2. Synthesizing suitable linker-recognition units;

3. Developing a method to link these linker-recognition units with epothilones to conjugates.

This invention correspondingly comprises conjugates of general formula I



I,

in which

R^{1a}, R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_m$ group, in which m is 2 to 5,

R^{2a}, R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n$ group, in which n is 2 to 5, or C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

R^{4a}, R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p$ group, in which p is 2 to 5,

R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2Oalkyl, CH_2Oacyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6, R^7, in each case, are hydrogen, or together an additional bond or together an

oxygen atom, or together an NH group, or together an N-alkyl group, or together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH),  , O-CH_2, or, if G represents a CH_2 group, is CH_2-O,

W is a group C(=X)R^8, or a bi- or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, forms a group O-L^4 with the latter, or, if a radical in W contains an amino group, forms a group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group, which should be straight-chain or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10}, R^{11}, in each case independently of one another, are hydrogen, C_1-C_{20} alkyl, aryl, or aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z can represent oxygen or H/OR^{12},

R^{12} can represent hydrogen or a protective group PG^Z,

A-Y can represent a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or

NR^{21}-SO_2,

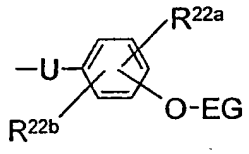
R^{20} can represent C_1-C_{20} alkyl,

R^{21} can represent a hydrogen atom or C_1-C_{10} alkyl,

L^1, L^2, L^4, independently of one another, can represent hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker-recognition unit of general formula III;

with the condition that at least one substituent L^1, L^2 or L^4 represents a linker-recognition unit of general formula (III);

the linker-recognition unit of general formula (III) has the following structure,



III,

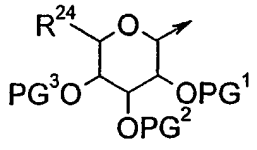
in which

R^{22a}, R^{22b}, independently of one another, can represent hydrogen, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy, aryl, aralkyl, hydroxy, alkoxy, CO_2H, CO_2alkyl, halogen, CN, NO_2, NH_2, or N_3,

U can represent -C(=O)NR^{23}-, -C(=S)NR^{23}-, -C(=O)NR^{23}-CH_2-, -C(=S)NR^{23}-CH_2-, -C(=O)O-, -C(=S)O-, -C(=O)O-CH_2-, -C(=S)O-CH_2-,

R^{23} can represent hydrogen or C_1-C_{10} alkyl, and

EG is a recognition unit of general formula IV,



IV,

in which

R^{24} can represent a group CH_2OPG^4 or a group CO_2R^{26},

PG^1, PG^2, PG^3, and PG^4, independently of one another, can represent hydrogen or a protective group PG,

R^{26} can represent hydrogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_4-C_7 cycloalkyl, which can contain an oxygen atom, aryl, aralkyl, tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, or tris(aralkyl)-silyl,

PG^X, PG^Y, and PG^Z can represent a protective group PG,

as a uniform isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

According to this invention, the above-mentioned conjugates can comprise one or more recognition units; in this case, the recognition units that are related to a conjugate can be identical or different. It is preferred that the recognition units of a conjugate be identical.

The compounds of general formula I can be used in the form of their α-, β- or γ-cyclodextrin clathrates or their substituted α-, β- or γ–cyclodextrin clathrates or in the form of liposomal or PEGylated compositions.

The conjugates according to the invention are preferably used for the treatment of diseases that are linked with proliferative processes. For example, the therapy of widely varying tumors, the therapy of inflammatory and/or neurodegenerative diseases,

such as multiple sclerosis or Alzheimer's disease, the therapy of angiogenesis-associated diseases, such as the growth of solid tumors, rheumatoid arthritis or diseases of the ocular fundus can be mentioned.

Especially preferred is the use of the conjugates according to the invention for the treatment of primary tumors and/or metastases that are not operatively accessible, either as monotherapy or in combination with substances that increasingly trigger cell death (apoptosis) and necrosis, so that when cells decompose, it results in an elevated release of normally intracellular, lysosomal enzymes, such as, e.g., glucuronidase, which results in a stronger reaction of the conjugates according to the invention. For example, in this connection, substances that are used for the so-called "vascular targeting" can be mentioned. These substances result in destruction in particular of the tumor endothelium, which subsequently results in an increased necrosis of the tumor because of the deficient nutrient supply. For example, L19 constructs, such as, for example, the EDB fibronectin or combrestatin A4-prodrugs, can be mentioned here.

The production of epothilones, their precursors and derivatives of general formula II is carried out according to the methods that are known to one skilled in the art, as they are described in, for example, DE 19907588, WO 98/25929, WO 99/58534, WO 99/2514, WO 99/67252, WO 99/67253, WO 99/7692, EP 99/4915, WO 00/485, WO 00/1333, WO 00/66589, WO 00/49019, WO 00/49020, WO 00/49021, WO 00/71521, WO 00/37473, WO 00/57874, WO 01/92255, WO 01/81342, WO 01/73103, WO 01/64650, WO 01/70716, US 6204388, US 6387927, US 6380394, US 02/52028, US 02/58286, US 02/62030, WO 02/32844, WO 02/30356, WO 02/32844, WO 02/14323, and WO 02/8440.

As alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{20}, R^{21}, R^{22a}, R^{22b}, R^{23}, R^{25}, R^{26} and R^{27}, straight-chain or branched-chain alkyl groups with 1-20 carbon atoms can be considered, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, and decyl.

Alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{20}, R^{21}, R^{22a}, R^{22b}, R^{25}, R^{26} and R^{27} can also be perfluorinated or substituted by 1-5 halogen atoms, hydroxy groups, C_1-C_4-alkoxy groups, or C_6-C_{12}-aryl groups (which can be substituted by 1-3 halogen atoms).

As aryl radicals R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22a}, R^{22b}, R^{26} and R^{27}, substituted and unsubstituted carbocyclic or heterocyclic radicals with one or more heteroatoms, such as phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl, thiazolyl, benzothiazolyl, benzoxazolyl, which can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl, C_1-C_{20}-acyloxy groups, are suitable. The heteroatoms can be oxidized if as a result the aromatic character is not lost, such as, for example, the oxidation of a pyridyl to a pyridyl-N-oxide.

As bi- and tricyclic aryl radicals W, substituted and unsubstituted carbocyclic or heterocyclic radicals with one or more heteroatoms, such as naphthyl, anthryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, benzoxazinyl,

benzofuranyl, indolyl, indazolyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thienopyridinyl, pyridopyridinyl, benzopyrazolyl, benzotriazolyl, or dihydroindolyl, which can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl, or C_1-C_{20}-acyloxy groups, are suitable. The heteroatoms can be oxidized if as a result the aromatic character is not lost, such as, for example, the oxidation of a quinolyl to a quinolyl-N-oxide.

The aralkyl groups in R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22a}, R^{22b}, R^{26} and R^{27} can contain in the ring up to 14 C atoms, preferably 6 to 10 C atoms, and in the alkyl chain 1 to 8, preferably 1 to 4 atoms. As aralkyl radicals, for example, benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl, and pyridylpropyl are considered. The rings can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl, or C_1-C_{20}-acyloxy groups.

As representatives of protective groups PG, tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, tris(aralkyl)-silyl, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_4-C_7-cycloalkyl, which in addition can contain an oxygen atom in the ring, aryl, C_7-C_{20}-aralkyl, C_1-C_{20}-acyl, aroyl, C_1-C_{20}-alkoxycarbonyl, C_1-C_{20}-alkylsulfonyl as well as arylsulfonyl can be mentioned.

As alkyl, silyl and acyl radicals for protective groups PG, in particular the radicals that are known to one skilled in the art are considered. Preferred are the alkyl or

silyl radicals that are easily cleavable from the corresponding alkyl ethers and silyl ethers, such as, for example, the methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, or para-methoxybenzyl radical as well as alkylsulonyl and arylsulfonyl radicals. As an alkyoxycarbonyl radical, e.g., trichloroethyloxycarbonyl (Troc) is suitable. As acyl radicals, e.g., formyl, acetyl, propionyl, isopropionyl, trichloromethylcarbonyl, pivalyl, and butyryl or benzoyl, which can be substituted with amino groups and/or hydroxy groups, are suitable.

As amino protective groups PG, the radicals that are known to one skilled in the art are considered. For example, the Alloc, Boc, Z, benzyl, f-Moc, Troc, Stabase or benzostabase group can be mentioned.

As halogen atoms, fluorine, chlorine, bromine or iodine is considered.

The acyl groups can contain 1 to 20 carbon atoms, whereby formyl, acetyl, propionyl, isopropionyl and pivalyl groups are preferred.

The C_2-C_{10}-alkylene-α,ω-dioxy group that is possible for X is preferably an ethyleneketal or neopentylketal group.

As preferred recognition units EG, those are considered that, for example, by overexpression of suitable enzymes in proliferating tissues can be cleaved from the latter. For example, glucuronidase can be mentioned here.

Preferred compounds of general formula I are those in which A-Y represents O-C(=O) or NR^{21}-C(=O); D-E represents an H_2C-CH_2 group or an HC=CH group; G represents a CH_2 group; Z represents an oxygen atom; R^{1a}, R^{1b} in each case represent C_1-C_{10} alkyl or together a $-(CH_2)_p$ group with p equal to 2 or 3 or 4; R^{2a}, R^{2b}, independently of one another, represent hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl; R^3 represents hydrogen; R^{4a}, R^{4b}, independently of one another, represent hydrogen or C_1-C_{10} alkyl; R^5 represents hydrogen or C_1-C_4 alkyl or CH_2OH or CH_2NH_2 or $CH_2N(alkyl, acyl)_{1,2}$ or CH_2Hal; R^6 and R^7 together represent an additional bond or together an oxygen atom or together an NH group or together an N-alkyl group or together a CH_2 group; W represents a group $C(=X)R^8$ or a 2-methylbenzothiazol-5-yl radical or a 2-methylbenzoxazol-5-yl radical or a quinolin-7-yl radical or a 2-aminomethylbenzothiazol-5-yl radical or a 2-hydroxymethylbenzothiazol-5-yl radical or a 2-aminomethylbenzoxazol-5-yl radical or a 2-hydroxymethylbenzoxazol-5-yl radical; X represents a $CR^{10}R^{11}$ group; R^8 represents hydrogen or C_1-C_4 alkyl or a fluorine atom or a chlorine atom or a bromine atom; R^{10}/R^{11} represent hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl or hydrogen/2-methyloxazol-4-yl or hydrogen/2-aminomethylthiazol-4-yl or hydrogen/2-aminomethyloxazol-4-yl or hydrogen/2-hydroxymethylthiazol-4-yl or hydrogen/2-hydroxymethyloxazol-4-yl.

In a preferred embodiment, radicals R^{22a} and R^{22b} are selected from the group that consists of C_1-C_8-alkyl, C_1-C_8-alkoxy, halogen, nitro, CN, N_3, NH_2 and CO_2-(C_1-C_8-alkyl). Especially preferred in this connection are the radicals methyl, ethyl, propyl, i-propyl, t-butyl, CF_3, C_2F_5, F, Cl, nitro, CN, N_3, NH_2, CO_2-methyl, CO_2-ethyl, CO_2-propyl and CO_2-i-propyl.

In another preferred embodiment, radical R^{26} is selected from the group that consists of C_1-C_8-alkyl and C_2-C_8-alkenyl. Especially preferred in this connection are the radicals methyl, ethyl, propyl, i-propyl, t-butyl, CF_3, propenyl and butenyl.

In another preferred embodiment, radicals R^{2a} and R^{2b} are selected such that one of radicals R^{2a} or R^{2b} represents hydrogen, while the other radical in each case is selected from the group that consists of C_1-C_7-alkyl, C_2-C_7-alkenyl and C_2-C_7-alkinyl. Especially preferred in this connection are the radicals methyl, ethyl, propyl, i-propyl, propenyl, butenyl, propinyl and butinyl.

The compounds that are mentioned below are especially preferred according to the invention as effector elements:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

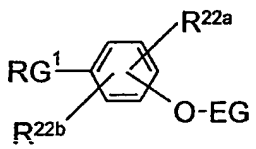
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione.

In a compound of general formula (I) according to the invention that contains one of the above-mentioned elements, the hydrogen atoms in the above-mentioned elements are replaced by radicals L^1-L^3 in the positions indicated in formula (I), whereby radicals L^1-L^3 have the above-indicated meanings.

The invention also relates to linker-recognition units of general formula III^1:



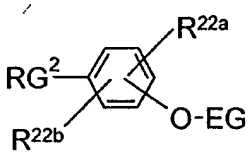
III^1,

in which

RG^1 represents an O=C=N group or an S=C=N group or an O=C=N-CH_2 group or an S=C=N-CH_2 group; and

R^{22a}, R^{22b} and EG have the above-indicated meanings;

as well as linker-recognition units of general formula III^2:



III^2,

in which

RG^2 represents an HO-CH_2 group or an HNR^{23}-CH_2 group; and

R^{22a}, R^{22b} and EG have the above-mentioned meanings;

but with the condition that the following compounds are not included:

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(2-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(4-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside;

(2-Hydroxymethyl-4-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(4-Hydroxymethyl-2-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

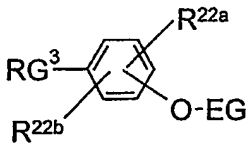
(2-Hydroxymethyl-4-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl-2-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Chloro-4-hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

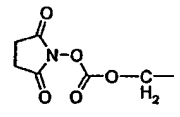
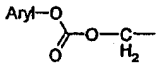
(2-Chloro-4-hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

as well as linker-recognition units of general formula III^3:



III^3,

in which

RG^3 represents a Hal-C(=O)-CH_2 group or a Hal-C(=S)-CH_2 group or an R^{27}-C(=O)-O-C(=O)-CH_2 group or an R^{27}-C(=O)-O-C(=S)-CH_2 group or a  group or a  group;

R^{27} is C_1-C_{10} alkyl, aryl or aralkyl; and

R^{22a}, R^{22b} and EG have the above-mentioned meanings;

but with the condition that the following compounds are not included:

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)-methyluronate)benzyl]carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)benzyl]-carbonate;

4-Nitrophenyl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-5-nitrobenzyl]-carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate;

4-Nitrophenyl-[4-methoxy-5-nitro-2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)benzyl]carbonate;

4-Nitrophenyl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate;

4-Chlorophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate.

The invention also relates to processes

for reacting a linker-recognition unit of general formula III^1 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker-recognition unit need not be met, and L^1 and/or L^2 and/or L^4 have the meaning of a hydrogen atom, and free hydroxyl groups and/or amino groups that are not required for the reaction optionally are protected,

for reacting a linker-recognition unit of general formula III^2 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker-recognition unit need not be met, and L^1 and/or L^2 and/or L^4 have the meaning of a C(=O)Hal group or a C(=S)Hal group, and free hydroxyl groups and/or amino groups that are not required for the reaction are optionally protected,

for reacting a linker-recognition unit of general formula III^3 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker-recognition unit need not be met, and L^1 and/or L^2 and/or L^4 have the meaning of a hydrogen atom, and free hydroxyl groups and/or amino groups that are not required for the reaction are optionally protected.

The invention also relates to the use of a compound of general formula I, whereby the substituents have the above-mentioned meanings, but the condition that at least one substituent L^1, L^2 or L^4 represent a linker of general formula III need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(S)Cl , in a process as described above.

The invention also relates to the use of a compound of general formula I, whereby the substituents have the above-mentioned meanings, but the condition that at least one substituent L^1, L^2 or L^4 represent a linker of general formula III need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(S)Cl, for the production of an effector recognition unit conjugate as described above.

The invention also relates to the use of a linker-recognition unit of general formula III^1, III^2 or III^3 for the production of an effector-recognition unit conjugate, as described above.

The invention also relates to the use of a linker-recognition unit of general formula III^1, III^2 or III^3 in one of the processes according to the invention for the production of an effector-recognition unit conjugate as described above.

The invention also relates to the conjugates according to the invention that contain effectors, linkers and recognition units for use as medications or for the production of a medication or a pharmaceutical composition.

The invention also relates to the use of the conjugates according to the invention for the production of medications for the treatment of diseases that are linked with proliferative processes, such as tumors, inflammatory and/or neurodegenerative diseases, multiple sclerosis, Alzheimer's disease, or for the treatment of angiogenesis-associated diseases, such as the growth of solid tumors, rheumatoid arthritis, or diseases of the ocular fundus.

The invention also relates to the use of the conjugates according to the invention for the production of medications for the treatment of primary tumors and/or metastases that are not operatively accessible, either as monotherapy or in combination with substances that increasingly trigger cell death (apoptosis) and necrosis, so that when

tumor cells decompose, it results in an elevated release of normally intracellular, lysosomal enzymes, such as, e.g., glucuronidase, which results in a stronger reaction of the above-mentioned conjugates.

Treatment or administration in combination with the above-mentioned substances in this case comprises the simultaneous (both in the mixture and in separate doses) but also the respectively separate administration of the individual components of the combination, for example an alternating administration, as well as administration schemes, in which one component is given as a long-term medication, and the other component is administered in addition at regular or irregular intervals for shorter periods. In this case, the components of the combination can be fed via the same or via different administration paths. In the above-mentioned administrations in combination are preferably those in which the components of the combination achieve an additive action; especially preferred are those administration schemes in which a synergistic action is set.

With respect to a combination administration with the conjugates according to the invention, for example, substances can be mentioned that are used for the so-called "vascular targeting." These substances result in destruction especially of tumor endothelium, which subsequently results in an elevated necrosis of the tumor because of the deficient supply of nutrients. For example, L19 constructs, such as, for example the EDB–fibronectin or combrestatin A4-prodrugs, can be mentioned here.

Examples of the Synthesis of Linker-Recognition Units (LE)

Example LE1

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-hydroxymethyl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

Example LE1a

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-formyl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

The solution of 5.0 g (12.6 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxyclic acid methyl ester in 90 ml of acetonitrile is mixed with 2.1 g of 4-hydroxy-3-nitrobenzaldehyde, 3.58 g of silver(I) oxide, and it is stirred for 16 hours at 23°C. It is filtered over Celite, and the residue that is obtained after removal of the solvent is purified by chromatography on fine silica gel. 5.72 g (11.8 mmol, 94%) of the title compound is isolated.

Example LE1

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-hydroxymethyl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

The solution of 5.72 g (11.8 mmol) of the compound, presented according to Example LE1a, in a mixture that consists of 110 ml of tetrahydrofuran and 22 ml of methanol is mixed at 0°C with 224 mg of sodium borohydride, and it is stirred for 30 minutes. It is mixed with saturated ammonium chloride solution, diluted with water and extracted several times with ethyl acetate. The combined organic extracts are washed

with saturated sodium chloride solution, dried on sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 5.62 g (11.6 mmol, 98%) of the title compound is isolated.

^{1}H-NMR (d_6-DMSO): δ = 1.99+2.02 (9H), 3.64 (3H), 4.51 (2H), 4.73 (1H), 5.07 (1H), 5.12 (1H), 5.43 (1H), 5.48 (1H), 5.71 (1H), 7.38 (1H), 7.62 (1H), 7.80 (1H) ppm.

Example LE2

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(2-hydroxymethyl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

Example LE2a

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(2-formyl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

Analogously to Example LE1a, 5.0 g (12.6 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxylic acid methyl ester is reacted with 2-hydroxy-3-nitrobenzaldehyde, and after working-up and purification, 4.31 g (8.92 mmol, 71%) of the title compound is isolated.

Example LE2

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(2-hydroxymethyl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

Analogously to Example LE1, 1.0 g (2.07 mmol) of the compound that is presented according to Example LE2a is reacted, and after working-up and purification, 921 mg (1.90 mmol, 92%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 2.06 (3H), 2.08 (3H), 2.10 (3H), 2.53 (1H), 3.71 (3H), 4.25 (1H), 4.61 (1H), 4.72 (1H), 5.27-5.44 (4H), 7.09 (1H), 8.18 (1H), 8.30 (1H) ppm.

Example LE3

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-hydroxymethyl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Example LE3a

2-[1,3]Dioxolan-2-yl-4-nitro-phenol

The solution of 25 g (149.6 mmol) of 2-hydroxy-5-nitrobenzaldehyde in 500 ml of toluene is mixed with 100 ml of ethylene glycol, 2.85 g of p-toluenesulfonic acid monohydrate, and it is refluxed in a water separator for 5 hours. After cooling, it is poured into saturated sodium bicarbonate solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried on sodium sulfate. The residue that is obtained after filtration and removal of the solvent is further reacted without purification.

Example LE3b

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(2-[1,3]dioxolan-2-yl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

20.0 g (50.4 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxylic acid methyl ester is reacted analogously to Example LE1a with the compound that is presented according to Example LE3a, and after working-up and purification, 21.9 g (41.5 mmol, 82%) of the title compound is isolated.

Example LE3c

(2S,3S,4S,5R,6S)-6-(2-[1,3]Dioxolan-2-yl-4-nitro-phenoxy)-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid methyl ester

The solution of 21.85 g (41.5 mmol) of the compound, presented according to Example LE3b, in 1.17 l of methanol is mixed at 0°C with the solution of 2.42 g of sodium methanolate in 45 ml of methanol, and it is stirred for 3 more hours. It is mixed with 9.14 g of citric acid hydrate and concentrated by evaporation. The residue is dissolved in a mixture that consists of ethyl acetate and methanol, filtered over a short silica gel layer, and 16.6 g (41.4 mmol, 99%) of the title compound is isolated after removal of the solvent.

Example LE3d

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-[1,3]dioxolan-2-yl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

The solution of 8.0 g (19.9 mmol) of the compound, presented according to Example LE3c, in 560 ml of dichloromethane, is mixed with 22.9 ml of *tert*-butyl-dimethyl-silyltriflate as well as 23.8 ml of 2,6-lutidine, and it is stirred for 24 hours at 23°C. It is poured into water, extracted several times with dichloromethane, the combined organic extracts are washed with saturated sodium chloride solution and dried

on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel, and 9.90 g (13.3 mmol, 67%) of the title compound as well as 2.17 g (29.2 mmol, 15%) of a stereoisomer are isolated.

Example LE3e

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-[1,3]dioxolan-2-yl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid

The solution of 5.64 g (7.58 mmol) of the compound, presented according to Example LE3d, in 150 ml of allyl alcohol is mixed with 9.1 ml of a 1 M solution of sodium allyl alcoholate in allyl alcohol, and it is stirred for 2.5 hours at 50°C. It is concentrated by evaporation, mixed with water, extracted several times with dichloromethane, the combined organic extracts are washed with saturated sodium chloride solution and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel, and 1.78 g (2.44 mmol, 32%) of the title compound as well as 1.87 g (2.43 mmol, 32%) of (2R,3S,4S,5R,6S)-3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-[1,3]dioxolan-2-yl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester are isolated.

Example LE3f

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-[1,3]dioxolan-2-yl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 1.35 g (1.85 mmol) of the compound, presented according to Example LE3e, in 5 ml of dimethylformamide is mixed with 0.3 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene as well as 0.176 ml of allyl bromide, and it is stirred for

16 hours at 23°C. It is poured into water, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel, and 1.03 g (1.34 mmol, 72%) of the title compound is isolated.

Example LE3g

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-formyl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 50 mg (61.6 µmol) of the compound, presented according to Example LE3f, in 2 ml of acetone is mixed with 12.9 mg of p-toluenesulfonic acid monohydrate, and it is stirred for 24 hours at 23°C. It is poured into saturated sodium bicarbonate solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel, and 25.9 mg (35.7 µmol, 58%) of the title compound is isolated.

Example LE3

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-hydroxymethyl-4-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

720 mg (0.99 mmol) of the compound that is presented according to Example LE3g is reacted analogously to Example LE1, and after working-up, 710 mg (0.975

mmol, 98%) of the title compound, which is further reacted without purification, is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.05-0.15 (18H), 0.85-0.94 (27H), 2.97 (1H), 3.87 (1H), 3.99 (1H), 4.36 (1H), 4.41 (1H), 4.52 (1H), 4.58 (2H), 5.01 (1H), 5.22 (1H), 5.28 (1H), 5.61 (1H), 5.85 (1H), 7.07 (1H), 8.18 (1H), 8.33 (1H) ppm.

Example LE4

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Example LE4a

4-[1,3]Dioxolan-2-yl-2-nitro-phenol

Analogously to Example LE3a, 25 g (149.6 mmol) of 4-hydroxy-3-nitrobenzaldehyde is reacted, and after working-up, 27.6 g (131 mmol, 87%) of the title compound is isolated.

Example LE4b

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-[1,3]dioxolan-2-yl-2-nitro-phenoxy)-tetrahydro-pyran-2- carboxylic acid methyl ester

23.4 g (59.0 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxylic acid methyl ester is reacted analogously to Example LE1a with the compound that is presented according to Example LE4a, and after working-up and purification, 24.5 g (46.4 mmol, 79%) of the title compound is isolated.

Example LE4c

(2S,3S,4S,5R,6S)-6-(4-[1,3]Dioxolan-2-yl-2-nitro-phenoxy)-3,4,5-trihydroxy-tetrahydro-pyran-2- carboxylic acid methyl ester

358 mg (679 µmol) of the compound that is presented according to Example LE4b is reacted analogously to Example LE3c, and after working-up, 270 mg (673 µmol, 99%) of the title compound is isolated.

Example LE4d

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-[1,3]dioxolan-2-yl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

268 mg (668 µmol) of the compound that is presented according to Example LE4c is reacted analogously to Example LE3d, and after working-up and purification, 183 mg (246 µmol, 37%) of the title compound is isolated.

Example LE4e

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-[1,3]dioxolan-2-yl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid

The solution of 5.0 g (6.72 mmol) of the compound, presented according to Example LE4d, in 130 ml of methanol is mixed with 3.6 ml of water, heated to 70°C and mixed with 3.01 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene. It is allowed to react for 4 more hours, set at a pH of 3 by adding 1N hydrochloric acid, and extracted several times with ethyl acetate. The combined organic extracts are washed with water and saturated sodium chloride solution and dried on sodium sulfate. The residue that is obtained after

filtration and removal of the solvent is purified by chromatography on fine silica gel, and 1.53 g (2.10 mmol, 31%) of the title compound is isolated.

Example LE4f

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-[1,3]dioxolan-2-yl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

2.87 g (3.93 mmol) of the compound that is presented according to Example LE4e is reacted analogously to Example LE3f, and after working-up and purification, 2.51 g (3.26 mmol, 83%) of the title compound is isolated.

Example LE4g

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-formyl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

2.51 g (3.26 mmol) of the compound that is presented according to Example LE4f is reacted analogously to Example LE3g, and after working-up, 2.35 g (3.24 mmol, 99%) of the title compound, which is further reacted with purification, is isolated.

Example LE4

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-2-nitro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

2.23 g (3.07 mmol) of the compound that is presented according to Example LE4g is reacted analogously to Example LE1, and after working-up and purification, 2.12 g (2.91 mmol, 95%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.00 (3H), 0.07 (3H), 0.12-0.17 (12H), 0.83 (9H), 0.87 (9H), 0.92 (9H), 1.83 (1H), 3.85 (1H), 4.05 (1H), 4.40 (1H), 4.51 (1H), 4.60 (2H), 4.70 (2H), 5.22 (1H), 5.30 (1H), 5.58 (1H), 5.87 (1H), 7.17 (1H), 7.52 (1H), 7.83 (1H) ppm.

Example LE5

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Example LE5a

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-formyl-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

44.1 g (111 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxylic acid methyl ester is reacted analogously to Example LE1a with 14 g of 4-hydroxy-benzaldehyde, and after working-up and purification, 35.1 g (80 mmol, 72%) of the title compound is isolated.

Example LE5b

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-hydroxymethyl-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

16.5 g (37.7 mmol) of the compound that is presented according to Example LE5a is reacted analogously to Example LE1, and after working-up, 17.4 g (max. 37.7 mmol) of the title compound, which is further reacted without being purified, is isolated.

Example LE5c

(2S,3S,4S,5R,6S)-3,4,5-Trihydroxy-6-(4-hydroxymethyl-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

17.4 g (max. 37.7 mmol) of the compound that is presented according to Example LE5b is reacted analogously to Example LE3c, and after working-up, 13.9 g (max. 37.7 mmol) of the title compound, which is further reacted without being purified, is isolated.

Example LE5d

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-*tert*-butyl-dimethyl-silanyloxymethyl-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

13.9 g (max. 37.7 mmol) of the compound that is presented according to Example LE5c is reacted analogously to Example LE3d, and after working-up and purification, 21.5 g (27.9 mmol, 74%) of the title compound is isolated.

Example LE5e

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-*tert*-butyl-dimethyl-silanyloxymethyl-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 21.5 g (27.9 mmol) of the compound, presented according to Example LE5d, in 103 ml of allyl alcohol is mixed with 9.9 ml of titanium(IV)-tetraisopropoxide, and it is heated for 21 hours under an atmosphere of dry argon to 110°C. After cooling, it is mixed with water, diluted with ethyl acetate, filtered over Celite, and the organic phase is separated. The aqueous phase is extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium

chloride solution, and it is dried on sodium sulfate. After filtration and removal of the solvent, 22.6 g (max. 27.9 mmol) of the title compound, which is further reacted without being purified, is isolated.

Example LE5

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 22.6 g (max. 27.9 mmol) of the compound, presented according to Example LE5e, in a mixture that consists of 445 ml of dichloromethane and 218 ml of methanol is mixed at 0°C with 6.47 g of rac. camphor-10-sulfonic acid, and it is stirred for 1.5 hours at 0°C. It is mixed with a saturated sodium bicarbonate solution, diluted with water, extracted several times with dichloromethane, and the combined organic extracts are dried on sodium sulfate. After filtration, removal of the solvent and purification, 14.4 g (21.0 mmol, 75%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = -0.02 (3H), 0.07 (3H), 0.12 (3H), 0.14 (3H), 0.17 (6H), 0.85 (9H), 0.88 (9H), 0.92 (9H), 1.56 (1H), 3.86 (1H), 3.98 (1H), 4.37 (1H), 4.54 (1H), 4.62 (4H), 5.22 (1H), 5.31 (1H), 5.55 (1H), 5.89 (1H), 6.95 (2H), 7.28 (2H) ppm.

Example LE6

(2S,3S,4S,5R,6S)-4-Hydroxy-3,5-bis-triisopropylsilanyloxy-6-(4-hydroxymethyl-2-chloro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Example LE6a

2-Chloro-4-[1,3]dioxolan-2-yl-phenol

25 g (160 mmol) of 3-chloro-4-hydroxybenzaldehyde is reacted analogously to Example LE3a, and after working-up, 26.1 g (130 mmol, 81%) of the title compound, which is further reacted without being purified, is isolated.

Example LE6b

(2S,3S,4S,5R,6S)-6-(2-Chloro-4-[1,3]dioxolan-2-yl-phenoxy)-3,4,5-tris-acetoxy-tetrahydro-pyran-2-carboxylic acid methyl ester

29.1 g (73.3 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxylic acid methyl ester is reacted analogously to Example LE1a with 14.9 g of the compound that is presented according to Example LE6a, and after working-up and purification, 11.7 g (22.6 mmol, 31%) of the title compound is isolated.

Example LE6c

(2S,3S,4S,5R,6S)-6-(2-Chloro-4-[1,3]dioxolan-2-yl-phenoxy)-3,4,5-tris-hydroxy-tetrahydro-pyran-2-carboxylic acid methyl ester

25.3 g (48.9 mmol) of the compound that is presented according to Example LE6b is reacted analogously to Example LE3c, and after working-up, 17.2 g (44.0 mmol, 90%) of the title compound, which is further reacted without being purified, is isolated.

Example LE6d

(2S,3S,4S,5R,6S)-6-(2-Chloro-4-[1,3]dioxolan-2-yl-phenoxy)-4-hydroxy-3,5-bis-triisopropylsilanyloxy-tetrahydro-pyran-2-carboxylic acid methyl ester

17.2 g (44.0 mmol) of the compound that is presented according to Example LE6c is reacted analogously to Example LE3d with use of trifluoromethanesulfonic acid-triisopropylsilylester, and after working-up and purification, 18.1 g (25,7 mmol, 58%) of the title compound is isolated.

Example LE6e

(2S,3S,4S,5R,6S)-6-(2-Chloro-4-[1,3]dioxolan-2-yl-phenoxy)-4-hydroxy-3,5-bis-triisopropylsilanyloxy-tetrahydro-pyran-2-carboxylic acid

The solution of 18.1 g (25.8 mmol) of the compound, presented according to Example LE6d, in 400 ml of methanol is mixed with 13.9 ml of water, 7.7 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene, and it is stirred for 4 hours at 70°C. It is concentrated by evaporation, diluted with ethyl acetate and water, set at a pH of 2 with 4N hydrochloric acid, the separated organic phase is dried on sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography. 12.2 g (17.7 mmol, 69%) of the title compound is isolated.

Example LE6f

(2S,3S,4S,5R,6S)-6-(2-Chloro-4-[1,3]dioxolan-2-yl-phenoxy)-4-hydroxy-3,5-bis-triisopropylsilanyloxy-tetrahydro-pyran-2-carboxylic acid allyl ester

12.2 g (17.7 mmol) of the compound that is presented according to Example LE6e is reacted analogously to Example LE3f, and after working-up and purification, 12.9 g (17.7 mmol, 100%) of the title compound is isolated.

Example LE6g

(2S,3S,4S,5R,6S)-6-(2-Chloro-4-formyl-phenoxy)-4-hydroxy-3,5-bis-triisopropylsilanyloxy-tetrahydro-pyran-2-carboxylic acid allyl ester

12.9 g (17.7 mmol) of the compound that is presented according to Example LE6f is reacted analogously to Example LE3g, and after working-up, 12.0 g (17.5 mmol, 99%) of the title compound, which is further reacted without being purified, is isolated.

Example LE6

(2S,3S,4S,5R,6S)-4-Hydroxy-3,5-bis-triisopropylsilanyloxy-6-(4-hydroxymethyl-2-chloro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

12.0 g (17.5 mmol) of the compound, presented according to Example LE6f, is reacted analogously to Example LE1, and after working-up and purification, 11.4 g (16.6 mmol, 95%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.98-1.31 (42H), 1.64 (1H), 2.43 (1H), 3.67 (1H), 4.03 (1H), 4.10 (1H), 4.26 (1H), 4.54-4.64 (4H), 5.16-5.31 (3H), 5.84 (1H), 7.02 (1H), 7.19 (1H), 7.39 (1H) ppm.

Example LE7

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-2-methoxy-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Example LE7a

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-formyl-2-methoxy-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

Variant 1

8.0 g (20.1 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxylic acid methyl ester is reacted analogously to Example LE1a with 3.1 g of 4-hydroxy-3-methoxybenzaldehyde, and after working-up and purification, 3.2 g (6.8 mmol, 34%) of the title compound is isolated.

Variant 2

The solution of 5.0 g (12.6 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydropyran-2-carboxylic acid methyl ester in 150 ml of toluene is mixed with 20 g of 4-hydroxy-3-methoxybenzaldehyde, 30 ml of a 5N potassium hydroxide solution, 5.0 g of tetrabutylammonium hydrogen sulfate, and it is stirred for 2 days at 23°C. It is mixed with ethyl acetate and water, the organic phase is separated, and the aqueous phase is extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried on sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography. 1.94 g (4.14 mmol, 33%) of the title compound is isolated.

Example LE7b

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-hydroxymethyl-2-methoxy-phenoxy)-tetrahydropyran-2-carboxylic acid methyl ester

5.55 g (11.9 mmol) of the compound that is presented according to Example LE7a is reacted analogously to Example LE1, and after working-up and purification, 3.67 g (7.80 mmol, 66%) of the title compound is isolated.

Example LE7c

(2S,3S,4S,5R,6S)-3,4,5-Trihydroxy-6-(4-hydroxymethyl-2-methoxy-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

5.25 g (11.2 mmol) of the compound that is presented according to Example LE7b is reacted analogously to Example LE3c, and after working-up, 4.64 g (max. 11.2 mmol) of the title compound, which is further reacted without being purified, is isolated.

Example LE7d

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-*tert*-butyl-dimethyl-silanyloxymethyl-2-methoxy-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

4.64 g (max. 11.2 mmol) of the compound that is presented according to Example LE7c is reacted analogously to Example LE3d, and after working-up and purification, 8.43 g (10.5 mmol, 94%) of the title compound is isolated.

Example LE7e

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-*tert*-butyl-dimethyl-silanyloxymethyl-2-methoxy-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

8.43 g (10.5 mmol) of the compound that is presented according to Example LE7d is reacted analogously to Example LE5e, and after working-up, 8.38 g (10.1 mmol, 96%) of the title compound, which is further reacted without being purified, is isolated.

Example LE7

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-2-methoxy-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

8.38 g (10.1 mmol) of the compound that is presented according to Example LE7e is reacted analogously to Example LE5, and after working-up and purification, 5.92 g (8.3 mmol, 82%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = -0.04 (3H), 0.06 (3H), 0.12 (3H), 0.13 (3H), 0.16 (3H), 0.21 (3H), 0.84 (9H), 0.87 (9H), 0.92 (9H), 1.59 (1H), 3.82 (3H), 3.86 (1H), 4.01 (1H), 4.37 (1H), 4.52 (1H), 4.61 (4H), 5.21 (1H), 5.30 (1H), 5.52 (1H), 5.89 (1H), 6.83 (1H), 6.90 (1H), 6.92 (1H) ppm.

Example LE8

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-2-fluoro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Example LE8a

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-formyl-2-fluoro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

14.2 g (35.8 mmol) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-bromo-tetrahydro-pyran-2-carboxylic acid methyl ester is reacted analogously to Example LE1a with 5.05 g of 3-fluoro-4-hydroxybenzaldehyde, and after working-up and purification, 13.3 g (29.1 mmol, 81%) of the title compound is isolated.

Example LE8b

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-(4-hydroxymethyl-2-fluoro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

13.3 g (29.1 mmol) of the compound that is presented according to Example LE8a is reacted analogously to Example LE1, and after working-up, 13.3 g (29.0 mmol, 100%) of the title compound, which is further reacted withput being purified, is isolated.

Example LE8c

(2S,3S,4S,5R,6S)-3,4,5-Trihydroxy-6-(4-hydroxymethyl-2-fluoro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

11.2 g (29.0 mmol) of the compound that is presented according to Example LE8b is reacted analogously to Example LE3c, and after working-up, 11.2 g (max. 29.0 mmol) of the title compound, which is further reacted without being purified, is isolated.

Example LE8d

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-*tert*-butyl-dimethyl-silanyloxymethyl-2-fluoro-phenoxy)-tetrahydro-pyran-2-carboxylic acid methyl ester

11.2 g (max. 29.0 mmol) of the compound that is presented according to Example LE8c is reacted analogously to Example LE3d, and after working-up and purification, 18.5 g (23.4 mmol, 81%) of the title compound is isolated.

Example LE8e

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-*tert*-butyl-dimethyl-silanyloxymethyl-2-fluoro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

18.5 g (23.4 mmol) of the compound that is presented according to Example LE8d is reacted analogously to Example LE5e, and after working-up, 18.6 g (22.8 mmol, 97%) of the title compound, which is further reacted without being purified, is isolated.

Example LE8

(2S,3S,4S,5R,6S)-3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-hydroxymethyl-2-fluoro-phenoxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

18.6 g (22.8 mmol) of the compound that is presented according to Example LE8e is reacted analogously to Example LE5, and after working-up and purification, 13.3 g (19.0 mmol, 83%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = -0.02 (3H), 0.07 (3H), 0.12 (3H), 0.13 (3H), 0.17 (3H), 0.19 (3H), 0.84 (9H), 0.88 (9H), 0.92 (9H), 1.62 (1H), 3.86 (1H), 4.01 (1H), 4.38 (1H), 4.53 (1H), 4.61 (4H), 5.22 (1H), 5.31 (1H), 5.55 (1H), 5.90 (1H), 7.00 (1H), 7.02 (1H), 7.10 (1H) ppm.

Examples of the Synthesis of Effector-Linker Recognition Units (ELE)

Example ELE1

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester

Example ELE1a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione

The solution of 6.0 g (7.93 mmol) of (4S,7R,8S,9S,13Z,16S)-7-allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione, which was produced analogously to the process described in WO 00/66589, in 186 ml of anhydrous dichloromethane is mixed at 0°C with 26.4 ml of a 20% solution of trifluoroacetic acid in dichloromethane, and it is stirred for 6 hours at 0°C. It is poured into saturated sodium bicarbonate solution, extracted with dichloromethane, the combined organic extracts are washed with water and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 3.32 g (5.17 mmol, 65%) of the title compound is isolated as a colorless solid.

Example ELE1b

(4S,7R,8S,9S,13Z,16S)-Chloroformic acid-7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

The solution of 1.0 g (1.56 mmol) of the compound, presented according to Example ELE1a, in 20 ml of dichloromethane is mixed at 0°C with the solution of 285 mg of triphosgene in 6 ml of dichloromethane, 160 µl of pyridine, and it is stirred for 2.5 hours at 23°C. It is concentrated by evaporation, the residue is taken up in ethyl acetate, washed with water and saturated sodium chloride solution, and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 1.08 g (1.53 mmol, 98%) of the title compound is isolated.

Example ELE1c

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-{4-[(4S,7R,8S,9S,13Z,16S)7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester

The solution of 1.08 g (1.53 mmol) of the compound, presented according to Example ELE1b, in 30 ml of dichloromethane is mixed with 4.0 g of the compound that is presented according to Example LE1, 277 µl of triethylamine, and the suspension is stirred for 16 hours at 23°C. It is filtered, concentrated by evaporation, and the residue is purified by chromatography on fine silica gel. 408 mg (354 µmol, 23%) of the title compound is isolated.

Example ELE2

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester

The solution of 61 mg (58.7 µmol) of the compound, presented according to Example ELE 1, in 2 ml of dichloromethane is mixed at -50°C with 1.2 ml of a 0.1 M solution of dimethyldioxiram in acetone, and it is stirred for 1 hour. It is poured into a semiconcentrated sodium thiosulfate solution, extracted several times with dichloromethane, and the combined organic extracts are washed on sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on analytical thin-layer plates. 29 mg (27.5 µmol, 47%) of the title compound as well as 10 mg (9.5 µmol, 16%) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-{4-[(1R,3S,7S,10R,11S,12S,16S)-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.13 (3H), 1.16 (3H), 1.31 (3H), 1.34-1.88 (7H), 2.06 (6H), 2.12 (3H), 2.16-2.57 (6H), 2.71 (1H), 2.79 (3H), 2.84 (1H), 3.44 (1H), 3.69 (1H), 3.73 (3H), 4.22 (1H), 4.50 (1H), 4.71 (1H), 4.99-5.05 (2H), 5.19 (1H), 5.25-5.39 (3H), 5.45 (1H), 5.75 (1H), 6.07 (1H), 7.27 (2H), 7.32 (1H), 7.53 (1H), 7.78 (1H), 7.89 (1H) ppm.

Example ELE3

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-{2-[(4S,7R,8S,9S,13Z,16S)-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-4-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester

Example ELE3a

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-{2-[(4S,7R,8S,9S,13Z,16S)7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-4-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester

Analogously to Example ELE1c, 265 mg (376 µmol) of the compound that is presented according to Example ELE1b is reacted with the compound that is presented according to Example LE1, and after working-up and purification, 180 mg (156 µmol, 42%) of the title compound is isolated.

Example ELE3

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-{2-[(4S,7R,8S,9S,13Z,16S)-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-4-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester

Analogously to Example ELE1,173 mg (150 µmol) of the compound that is presented according to Example ELE3a is reacted, and after working-up and purification, 58 mg (55.8 µmol, 37%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.12 (3H), 1.13 (3H), 1.02-2.55 (13H), 1.70 (3H), 2.04 (3H), 2.07 (6H), 2.68 (1H), 2.76 (3H), 2.97 (1H), 3.39 (1H), 3.71 (1H), 3.73 (3H), 4.25 (1H), 4.65 (1H), 4.84 (1H), 5.00 (1H), 5.04 (1H), 5.16-5.38 (5H), 5.51 (1H), 5.72 (1H), 5.97 (1H), 7.08 (1H), 7.35 (1H), 7.79 (1H), 7.92 (1H), 7.98 (1H) ppm.

Example ELE4

(2S,3S,4S,5R,6S)-3,4,5-Triacetoxy-6-{2-[(1S,3S,7S,10R,11S,12S,16R)-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-4-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester

Analogously to Example ELE2, 151 mg (145 µmol) of the compound that is presented according to Example ELE3 is reacted, and after working-up and purification, 75 mg (71.1 µmol, 49%) of the title compound as well as 28 mg (26.5 µmol, 18%) of (2S,3S,4S,5R,6S)-3,4,5-triacetoxy-6-{2-[(1R,3S,7S,10R,11S,12S, 16S)-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-4-nitro-phenoxy}-tetrahydro-pyran-2-carboxylic acid methyl ester are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.08-1.84 (6H), 1.12 (3H), 1.17 (3H), 1.32 (3H), 2.07 (3H), 2.08 (6H), 2.08-2.17 (3H), 2.28-2.57 (4H), 2.71 (1H), 2.79 (3H), 2.84 (1H), 3.43 (1H), 3.71 (1H), 3.73 (3H), 4.27 (1H), 4.74 (1H), 4.81 (1H), 5.01 (1H), 5.05 (1H), 5.24-5.43 (5H), 5.73 (1H), 6.04 (1H), 7.11 (1H), 7.28 (1H), 7.80 (1H), 7.86 (1H), 8.03 (1H), 8.15 (1H) ppm.

Example ELE5

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

Example ELE5a

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE1c, 230 mg (312 µmol) of the compound that is presented according to Example ELE1b is reacted with 1.32 g of the compound that is presented according to Example LE4, and after working-up and purification, 132 mg (95 µmol, 30%) of the title compound is isolated.

Example ELE5

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 315 mg (226 µmol) of the compound, presented according to Example ELE5a, in a mixture that consists of 6.4 ml each of tetrahydrofuran and acetonitrile is mixed with 3.2 ml of hexafluorosilicic acid, 3.2 ml of HF-pyridine

complex, and it is stirred for 16 hours at 23°C. It is poured into saturated ammonium bicarbonate solution and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried on sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 116 mg (124 µmol, 55%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.13 (3H), 1.16 (3H), 1.31-2.75 (19H), 2.78 (3H), 2.91 (1H), 3.40 (1H), 3.71 (1H), 3.79 (2H), 3.94 (1H), 4.08 (1H), 4.60 (1H), 4.72 (2H), 4.75 (1H), 4.95-5.09 (3H), 5.16 (1H), 5.28 (1H), 5.36 (1H), 5.55 (1H), 5.71 (1H), 5.86-6.00 (2H), 7.21 (2H), 7.34 (1H), 7.54 (1H), 7.74 (1H), 7.91 (1H) ppm.

Example ELE6

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 50 mg (53 µmol) of the compound that is presented according to Example ELE5 is reacted, and after working-up and purification, 26 mg (27 µmol, 51%) of the title compound as well as 7 mg (7 µmol, 14%) of (2S,3S,4S,5R,6S)-6-{4-[(1R,3S,7S,10R,11S,12S,16S)-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester are isolated.

Example ELE7

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

The solution of 26 mg (27 µmol) of the compound, presented according to Example ELE6, in 0.7 ml of dichloromethane is mixed with 1 mg of tetrakis-triphenylphosphine-palladium (0), 4 µl of pyrrolidine, and it is stirred for 1 hour at 23°C. It is mixed with 300 µl of a 5% aqueous citric acid, extracted with dichloromethane, washed with water and saturated sodium chloride solution and dried on sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography, and 13.4 mg (15 µmol, 54%) of the title compound is isolated.

^{1}H-NMR (CD_3OD): δ = 1.04 (3H), 1.11 (3H), 1.25 (3H), 1.33 (3H), 1.40-1.83 (7H), 2.12 (2H), 2.37 (1H), 2.58-2.85 (3H), 2.83 (3H), 2.99 (1H), 3.44-3.60 (5H), 3.77 (2H), 4.64 (1H), ~4.95-5.07 (4H), 5.46 (1H), 5.77 (1H), 6.06 (1H), 7.33-7.45 (3H), 7.63 (1H), 7.86 (1H), 7.94 (1H) ppm.

Example ELE8

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Example ELE8a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione

The solution of 5.3 g (7.01 mmol) of (4S,7R,8S,9S,13Z,16S)-7-allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione, which was produced analogously to the process that is described in WO 00/66589, in a mixture that consists of 85 ml of tetrahydrofuran and 85 ml of acetonitrile is mixed with 31.7 ml of hexafluorosilicic acid, cooled to 0°C, 8.1 ml of trifluoroacetic acid is added in drops, and it is stirred for 20 hours at 0°C. It is poured into water, neutralized by adding a saturated sodium bicarbonate solution and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried on sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 2.82 g (4.39 mmol, 63%) of the title compound is isolated as a colorless solid.

^{1}H-NMR ($CDCl_3$): δ = -0.09 (3H), 0.08 (3H), 0.84 (9H), 1.08 (3H), 1.10 (3H), 1.12 (3H), 1.21-1.86 (5H), 1.70 (3H), 2.15 (1H), 2.29-2.97 (8H), 2.84 (3H), 3.14 (1H), 3.96 (1H), 4.03 (1H), 4.97-5.06 (2H), 5.23 (1H), 5.61 (1H), 5.77 (1H), 7.35 (1H), 7.79 (1H), 7.93 (1H) ppm.

Example ELE8b

(4S,7R,8S,9S,13Z,16S)-Chloroformic acid-7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Analogously to Example ELE1b, 1.0 g (1.56 mmol) of the compound that is presented according to Example ELE8a is reacted, and 1.05 g (1.49 mmol, 96%) of the title compound is isolated.

Example ELE8c

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE1c, 250 mg (350 µmol) of the compound that is presented according to Example ELE8b is reacted with 1.63 g of the compound that is presented according to Example LE4, and after working-up and purification, 260 mg (186 µmol, 53%) of the title compound is isolated.

Example ELE8

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE5, 321 mg (230 µmol) of the compound that is presented according to Example ELE8c is reacted, and after working-up and purification, 77 mg (82 µmol, 36%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.06 (3H), 1.24 (3H), 1.38-2.00 (7H), 1.70 (3H), 2.27-2.45 (4H), 2.50 (2H), 2.85 (4H), 2.96-3.49 (3H), 3.54 (1H), 3.77 (2H), 3.94

(1H), 4.05 (2H), 4.73 (2H), 4.89-5.01 (3H), 5.09-5.25 (4H), 5.29 (1H), 5.38 (1H), 5.70 (1H), 5.84 (1H), 5.93 (1H), 7.34 (1H), 7.40 (1H), 7.60 (1H), 7.79 (1H), 7.92 (1H), 7.98 (1H) ppm.

Example ELE9

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 82 mg (87 µmol) of the compound that is presented according to Example ELE8 is reacted, and after working-up and purification, 57 mg (60 µmol, 69%) of the title compound as well as 8 mg (8.4 µmol, 10%) of (2S,3S,4S,5R,6S)-6-{4-[(RS,3S,7S,10R,11S,12S,16S)-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester are isolated.

Example ELE10

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

The solution of 57 mg (60 µmol) of the compound, presented according to Example ELE9, in 1.8 ml of dichloromethane is mixed with 14.8 µl of phenylsilane, in

portions with a total of 2.9 mg of tetrakis-triphenylphosphine palladium (0), and it is stirred for 19 hours at 23°C. It is concentrated by evaporation, the residue that is obtained is purified by chromatography, and 27 mg (30 µmol, 49%) of the title compound is isolated.

^{1}H-NMR (DMSO-d6): δ = 0.91 (3H), 0.93 (3H), 1.07-2.75 (15H), 1.17 (3H), 1.23 (3H), 2.80 (3H), 2.93 (1H), 3.08-3.48 (4H), 3.61 (1H), 4.06 (1H), 4.87 (1H), 4.92 (1H), 4.99 (2H), 5.06 (1H), 5.14-5.25 (4H), 5.67 (1H), 5.96 (1H), 7.44 (1H), 7.48 (1H), 7.65 (1H), 7.90 (1H), 7.99 (2H) ppm.

Example ELE11

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Example ELE11a

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 1.7 g (2.41 mmol) of the compound, presented according to Example ELE1b, in 51 ml of toluene, is mixed with 10.7 g of the compound that is presented according to Example LE5, 210 mg of sodium bicarbonate, and it is stirred for 16 hours at 23°C. It is filtered, concentrated by evaporation, and the residue is purified

by chromatography on fine silica gel. 1.95 g (1.44 mmol, 60%) of the title compound is isolated.

Example ELE11

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 1.95 g (1.44 mmol) of the compound, presented according to Example ELE11a, in 87 ml of tetrahydrofuran is mixed in portions with a total of 7 ml of HF-pyridine complex over several hours, and it is stirred for a total of 24 hours at 23°C. It is poured into saturated ammonium bicarbonate solution and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried on sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 766 mg (857 µmol, 59%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.13 (6H), 1.18-1.89 (6H), 1.69 (3H), 2.18-2.54 (5H), 2.57 (1H), 2.66 (1H), 2.79 (3H), 2.88 (1H), 3.23 (1H), 3.36 (1H), 3.41 (1H), 3.66-3.95 (5H), 4.01 (1H), 4.56 (1H), 4.64-4.78 (3H), 4.93 (1H), 5.01 (1H), 5.05 (1H), 5.14 (1H), 5.26 (1H), 5.34 (1H), 5.57 (1H), 5.72 (1H), 5.84-5.97 (2H), 6.81 (2H), 6.94 (2H), 7.34 (1H), 7.74 (1H), 7.86 (1H) ppm.

Example ELE12

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 766 mg (857 µmol) of the compound that is presented according to Example ELE11 is reacted, and after working-up and purification, 616 mg (677 µmol, 79%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.11 (3H), 1.19 (3H), 1.31 (3H), 1.23-1.83 (6H), 1.96 (2H), 2.30-2.58 (4H), 2.68 (1H), 2.79 (1H), 2.81 (3H), 3.39-3.93 (10H), 4.61-4.79 (5H), 5.02 (1H), 5.06 (1H), 5.26 (1H), 5.34 (1H), 5.43 (1H), 5.72 (1H), 5.88 (1H), 5.97 (1H), 6.84 (2H), 7.05 (2H), 7.26 (1H), 7.76 (1H), 7.84 (1H) ppm.

Example ELE13

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

Analogously to Example ELE10, 320 mg (352 µmol) of the compound that is presented according to Example ELE12 is reacted, and after working-up and purification, 165 mg (190 µmol, 54%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 0.90 (3H), 0.98 (3H), 1.13 (3H), 1.23 (3H), 1.06-1.58 (5H), 1.67 (1H), 2.02 (1H), 2.09-2.31 (2H), 2.41-2.78 (4H), 2.80 (3H), 2.90 (1H),

3.06-3.40 (6H), 3.60 (1H), 4.66-4.80 (3H), 4.88-5.03 (4H), 5.18 (1H), 5.27 (1H), 5.69 (1H), 5.99 (1H), 6.95 (2H), 7.15 (2H), 7.34 (1H), 7.37 (1H), 7.88 (1H), 8.02 (1H) ppm.

Example ELE14

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Example ELE14a

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE11a, 1.95 g (2.77 mmol) of the compound that is presented according to Example ELE8b is reacted with the compound that is presented according to Example LE5, and after working-up and purification, 2.79 g (2.06 mmol, 75%) of the title compound is isolated.

Example ELE14

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE11, 2.78 g (2.06 mmol) of the compound that is presented according to Example ELE14a is reacted, and after working-up and purification, 1.00 g (1.12 mmol, 54%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.06 (3H), 1.13 (1H), 1.21 (3H), 1.48-1.96 (5H), 1.70 (3H), 2.25-2.54 (6H), 2.83 (3H), 2.87 (1H), 3.01 (1H), 3.10 (1H), 3.35 (1H), 3.46 (1H), 3.53 (1H), 3.74 (2H), 3.90 (1H), 3.98 (2H), 4.71 (2H), 4.86-5.00 (3H), 5.06-5.23 (4H), 5.27 (1H), 5.35 (1H), 5.69 (1H), 5.82 (1H), 5.91 (1H), 7.05 (2H), 7.33 (3H), 7.79 (1H), 7.95 (1H) ppm.

Example ELE15

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-11-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 1.30 g (1.45 mmol) of the compound that is presented according to Example ELE14 is reacted, and after working-up and purification, 1.15 g (1.26 mmol, 87%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 0.92 (3H), 0.93 (3H), 1.17 (3H), 1.19 (3H), 1.23-1.68 (7H), 2.04 (1H), 2.17 (1H), 2.28 (2H), 2.38 (1H), 2.62 (1H), 2.80 (3H), 2.93 (1H), 3.25-3.47 (3H), 3.60 (1H), 4.06 (1H), 4.10 (1H), 4.61 (2H), 4.87 (1H), 4.91 (1H), 4.99 (1H), 5.08 (2H), 5.11-5.22 (3H), 5.28 (1H), 5.32 (1H), 5.45 (1H), 5.51 (1H), 5.67 (1H), 5.88 (1H), 5.97 (1H), 7.03 (2H), 7.33 (2H), 7.47 (1H), 7.99 (2H) ppm.

Example ELE16

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-11-yloxycarbonyloxymethyl]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

Analogously to Example ELE10, 354 mg (389 µmol) of the compound that is presented according to Example ELE15 is reacted, and after working-up and purification, 187 mg (215 µmol, 55%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 0.92 (3H), 0.93 (3H), 1.18 (3H), 1.20 (3H), 1.00-1.68 (5H), 2.04 (1H), 2.16 (1H), 2.28 (2H), 2.38 (2H), 2.61 (1H), 2.80 (3H), 2.94 (1H), 3.07-3.40 (6H), 3.61 (1H), 4.07 (1H), 4.81 (1H), 4.88 (1H), 4.91-5.03 (3H), 5.09 (2H), 5.19 (1H), 5.21 (1H), 5.67 (1H), 5.96 (1H), 7.03 (2H), 7.32 (3H), 7.48 (1H), 7.99 (2H) ppm.

Example ELE17

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Example ELE17a

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,5-bis-triisopropylsilanyloxy)-4-hydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

The solution of 1.41 g (2.00 mmol) of the compound, presented according to Example ELE1b, in a mixture that consists of 40 ml of dimethylformamide and 16 ml of trichloromethane is mixed with 7.74 g of the compound that is presented according to Example LE6, 1.0 g of copper(I) chloride, and the suspension is stirred for 16 hours at 23°C. It is filtered, concentrated by evaporation, and the residue is purified by chromatography on fine silica gel. 770 mg (568 µmol, 28%) of the title compound is isolated.

Example ELE17

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE11, 1.54 g (1.14 mmol) of the compound that is presented according to Example ELE17a is reacted, and after working-up and purification, 612 mg (659 µmol, 58%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.14 (3H), 1.16 (3H), 1.70 (3H), 1.20-1.90 (5H), 2.18-2.59 (6H), 2.69 (1H), 2.77 (3H), 2.92 (1H), 3.14 (1H), 3.32 (1H), 3.37-3.53 (3H), 3.64-4.02 (5H), 4.54 (1H), 4.66-4.75 (3H), 4.86 (1H), 5.01 (1H), 5.06 (1H), 5.16 (1H), 5.28 (1H), 5.37 (1H), 5.56 (1H), 5.72 (1H), 5.90 (1H), 5.96 (1H), 6.88 (1H), 7.03 (1H), 7.08 (1H), 7.33 (1H), 7.74 (1H), 7.91 (1H) ppm.

Example ELE18

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 610 mg (657 µmol) of the compound that is presented according to Example ELE17 is reacted, and after working-up and purification, 517 g (547 µmol, 83%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.12 (3H), 1.18 (3H), 1.32 (3H), 1.07-1.83 (8H), 2.01-2.17 (2H), 2.29-2.59 (4H), 2.72 (1H), 2.80 (3H), 2.83 (1H), 3.45 (1H), 3.71 (2H), 3.81 (1H), 3.93 (1H), 3.95 (1H), 4.56 (1H), 4.63-4.75 (3H), 4.80 (1H), 5.02 (1H), 5.06 (1H), 5.27 (1H), 5.36 (1H), 5.46 (1H), 5.71 (1H), 5.92 (1H), 6.03 (1H), 6.94 (1H), 7.05 (1H), 7.10 (1H), 7.28 (1H), 7.76 (1H), 7.88 (1H) ppm.

Example ELE19

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

Analogously to Example ELE10, 310 mg (328 µmol) of the compound that is presented according to Example ELE18 is reacted, and after working-up and purification, 160 mg (177 µmol, 54%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 0.92 (3H), 0.98 (3H), 1.14 (3H), 1.22 (3H), 1.07-1.72 (7H), 2.02 (1H), 2.12-2.50 (4H), 2.55 (1H), 2.66 (1H), 2.73 (1H), 2.78 (3H), 2.92

(1H), 3.12 (1H), 3.24 (1H), 3.31 (3H), 3.38 (1H), 3.59 (1H), 4.70 (1H), 4.76 (1H), 4.88-5.02 (4H), 5.18 (1H), 5.28 (1H), 5.70 (1H), 6.00 (1H), 7.15 (2H), 7.25 (1H), 7.37 (1H), 7.88 (1H), 8.02 (1H)

Example ELE20

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Example ELE20a

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-4-hydroxy-3,5-bis-triisopropylsilanyloxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE17a, 2.13 g (3.02 mmol) of the compound that is presented according to Example ELE8b is reacted with the compound that is presented according to Example LE6, and after working-up and purification, 1.71 g (1.26 mmol, 42%) of the title compound is isolated.

Example ELE20

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-

yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE11, 930 mg (686 µmol) of the compound that is presented according to Example ELE20a is reacted, and after working-up and purification, 460 mg (495 µmol, 72%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.06 (3H), 1.14 (1H), 1.22 (3H), 1.51-1.95 (6H), 1.70 (3H), 2.28-2.43 (3H), 2.50 (2H), 2.84 (3H), 2.88 (1H), 2.98 (1H), 3.10 (1H), 3.23 (1H), 3.39 (1H), 3.53 (1H), 3.73 (1H), 3.82 (1H), 3.88-4.04 (3H), 4.72 (2H), 4.85 (1H), 4.92 (1H), 4.98 (1H), 5.10 (2H), 5.15 (1H), 5.21 (1H), 5.28 (1H), 5.36 (1H), 5.70 (1H), 5.82 (1H), 5.93 (1H), 7.20-7.28 (2H), 7.33 (1H), 7.44 (1H), 7.79 (1H), 7.95 (1H) ppm.

Example ELE21

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 610 mg (657 µmol) of the compound that is presented according to Example ELE20 is reacted, and after working-up and purification, 601 mg (636 µmol, 97%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.96 (3H), 1.03 (3H), 1.07-1.82 (8H), 1.23 (3H), 1.31 (3H), 2.15 (2H), 2.34 (2H), 2.52 (1H), 2.61 (1H), 2.71 (1H), 2.84 (3H), 3.04 (1H), 3.21 (1H), 3.45 (1H), 3.66-4.15 (6H), 4.30 (1H), 4.71 (2H), 4.85 (1H), 4.91 (1H), 4.96 (1H),

5.08 (1H), 5.21 (1H), 5.28 (1H), 5.35 (1H), 5.72 (1H), 5.92 (1H), 6.24 (1H), 7.23 (2H), 7.36 (1H), 7.42 (1H), 7.83 (1H), 8.00 (1H) ppm.

Example ELE22

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

Analogously to Example ELE10, 302 mg (320 µmol) of the compound that is presented according to Example ELE21 is reacted, and after working-up and purification, 178 mg (197 µmol, 62%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 0.93 (6H), 1.06-1.70 (6H), 1.18 (3H), 1.20 (3H), 2.05 (1H), 2.17 (1H), 2.21-2.47 (4H), 2.61 (1H), 2.80 (3H), 2.93 (1H), 3.11 (1H), 3.26 (2H), 3.32 (1H), 3.42 (1H), 3.62 (1H), 4.08 (1H), 4.85-5.04 (5H), 5.09 (2H), 5.20 (2H), 5.67 (1H), 5.96 (1H), 7.19-7.36 (3H), 7.45 (1H), 7.48 (1H), 7.99 (2H) ppm.

Example ELE23

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-methoxy-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Example ELE23a

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-methoxy-phenoxy}-3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE1c, 1.15 g (1.63 mmol) of the compound that is presented according to Example ELE1b is reacted with the compound that is presented according to Example LE7, and after working-up and purification, 1.44 g (1.04 mmol, 64%) of the title compound is isolated.

Example ELE23

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-methoxy-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE11, 1.44 g (1.04 mmol) of the compound that is presented according to Example ELE23a is reacted, and after working-up and purification, 386 mg (418 µmol, 40%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.13 (3H), 1.15 (3H), 1.31-1.90 (5H), 1.70 (3H), 2.25 (1H), 2.30-2.55 (4H), 2.58 (1H), 2.68 (1H), 2.74 (3H), 2.94 (1H), 3.40 (1H), 3.46-3.97 (8H), 3.79 (3H), 4.04 (1H), 4.56 (1H), 4.68-4.78 (4H), 5.00 (1H), 5.04 (1H), 5.16 (1H), 5.27 (1H), 5.35 (1H), 5.55 (1H), 5.71 (1H), 5.92 (2H), 6.57 (1H), 6.60 (1H), 7.06 (1H), 7.34 (1H), 7.73 (1H), 7.92 (1H) ppm.

Example ELE24

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-2-methoxy-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 384 mg (416 µmol) of the compound that is presented according to Example ELE23 is reacted, and after working-up and purification, 278 mg (296 µmol, 71%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.04 (3H), 1.11 (3H), 1.18 (3H), 1.32 (3H), 1.20-2.59 (13H), 2.70 (1H), 2.79 (4H), 3.17 (1H), 3.32 (1H), 3.44 (1H), 3.58-3.92 (6H), 3.82 (3H), 4.55-4.80 (5H), 5.01 (1H), 5.05 (1H), 5.28 (1H), 5.37 (1H), 5.44 (1H), 5.72 (1H), 5.91 (1H), 5.99 (1H), 6.69 (2H), 7.02 (1H), 7.26 (1H), 7.76 (1H), 7.87 (1H) ppm.

Example ELE25

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-2-methoxy-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

Analogously to Example ELE10, 100 mg (106 µmol) of the compound that is presented according to Example ELE24 is reacted, and after working-up and purification, 64 mg (71 µmol, 67%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 0.91 (3H), 0.98 (3H), 1.15 (3H), 1.23 (3H), 1.07-2.76 (11H), 2.79 (3H), 2.90 (1H), 3.05-3.42 (8H), 3.59 (1H), 3.72 (3H), 4.66-5.01 (7H),

5.09 (1H), 5.27 (1H), 5.71 (1H), 5.98 (1H), 6.75 (1H), 6.85 (1H), 7.00 (1H), 7.36 (2H), 7.88 (1H), 8.02 (1H) ppm.

Example ELE26

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-fluoro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Example ELE26a

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-methoxy-phenoxy}-3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE1c, 2.0 g (2.84 mmol) of the compound that is presented according to Example ELE1b is reacted with the compound that is presented according to Example LE8, and after working-up and purification, 2.06 g (1.50 mmol, 53%) of the title compound is isolated.

Example ELE26

(2S,3S,4S,5R,6S)-6-{4-[(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-

yloxycarbonyloxymethyl]-2-fluoro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE11, 2.06 g (1.50 mmol) of the compound that is presented according to Example ELE26a is reacted, and after working-up and purification, 1.01 g (1.11 mmol, 74%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.14 (6H), 1.20-2.61 (11H), 1.70 (3H), 2.68 (1H), 2.78 (3H), 2.91 (1H), 3.18-4.01 (10H), 4.56 (1H), 4.65-4.76 (3H), 4.90 (1H), 5.01 (1H), 5.06 (1H), 5.16 (1H), 5.27 (1H), 5.34 (1H), 5.55 (1H), 5.72 (1H), 5.89 (1H), 5.93 (1H), 6.73 (2H), 7.05 (1H), 7.33 (1H), 7.73 (1H), 7.88 (1H) ppm.

Example ELE27

(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-2-fluoro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid allyl ester

Analogously to Example ELE2, 1.01 g (1.11 mmol) of the compound that is presented according to Example ELE26 is reacted, and after working-up and purification, 657 mg (708 µmol, 64%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.04 (3H), 1.13 (3H), 1.32 (3H), 1.31 (3H), 1.24-1.84 (7H), 1.98-2.17 (2H), 2.29-2.59 (4H), 2.71 (1H), 2.80 (3H), 2.82 (1H), 3.29 (1H), 3.38 (1H), 3.45 (1H), 3.64-3.96 (6H), 4.59 (1H), 4.65-4.73 (3H), 4.83 (1H), 5.01 (1H), 5.06 (1H), 5.26 (1H), 5.34 (1H), 5.46 (1H), 5.71 (1H), 5.91 (1H), 6.01 (1H), 6.81 (2H), 7.04 (1H), 7.28 (1H), 7.75 (1H), 7.86 (1H) ppm.

Example ELE28

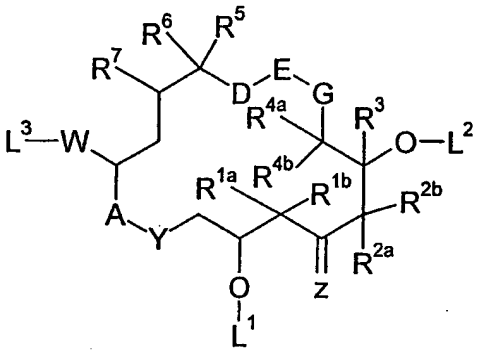
(2S,3S,4S,5R,6S)-6-{4-[(1S,3S,7S,10R,11S,12S,16R)-10-Allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]-heptadec-7-yloxycarbonyloxymethyl]-2-fluoro-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid

Analogously to Example ELE10, 350 mg (377 µmol) of the compound that is presented according to Example ELE27 is reacted, and after working-up and purification, 234 mg (264 µmol, 70%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 0.92 (3H), 0.98 (3H), 1.14 (3H), 1.23 (3H), 1.08-1.60 (7H), 1.66 (1H), 2.02 (1H), 2.11-2.75 (5H), 2.78 (3H), 2.91 (1H), 3.01-3.41 (5H), 3.60 (1H), 4.69 (1H), 4.77 (1H), 4.86 (1H), 4.89-5.02 (4H), 5.25 (1H), 5.28 (1H), 5.71 (1H), 5.99 (1H), 6.99 (1H), 7.06 (1H), 7.19 (1H), 7.26 (1H), 7.37 (1H), 7.87 (1H), 8.02 (1H) ppm.

Claims:

1. Conjugates of general formula (I):



I,

in which

R^{1a}, R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_m$ group, in which m is 2 to 5,

R^{2a}, R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n$ group, in which n is 2 to 5, or C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

R^{4a}, R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p$ group, in which p is 2 to 5,

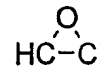
R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2Oalkyl, CH_2Oacyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6, R^7, in each case, are hydrogen, or together an additional bond or together an

oxygen atom, or together an NH group, or together an N-alkyl group, or together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH),  , O-CH_2, or, if G represents a CH_2 group, is CH_2-O,

W is a group C(=X)R^8, or a bi- or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, forms a group O-L^4 with the latter, or, if a radical in W contains an amino group, forms a group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group, which should be straight-chain or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10}, R^{11}, in each case independently of one another, are hydrogen, C_1-C_{20} alkyl, aryl, or aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z can represent oxygen or H/OR^{12},

R^{12} can represent hydrogen or a protective group PG^Z,

A-Y can represent a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or NR^{21}-SO_2,

R^{20} can represent C_1-C_{20} alkyl,

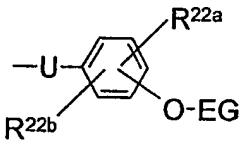
R^{21} can represent a hydrogen atom or C_1-C_{10} alkyl,

PG^X, PG^Y, and PG^Z can represent a protective group PG, and

L^1, L^2, L^4, independently of one another, can represent hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker-recognition unit of general formula (III);

with the condition that at least one substituent L^1, L^2 or L^4 represents a linker-recognition unit of general formula (III);

the linker-recognition unit of general formula (III) has the following structure,



III,

in which

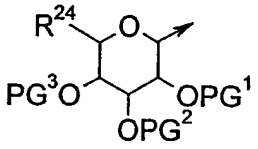
R^{22a}, R^{22b}, independently of one another, can represent hydrogen, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy, aryl, aralkyl, hydroxy, alkoxy, CO_2H, CO_2alkyl, halogen, CN, NO_2, NH_2, or N_3,

U can represent -C(=O)NR^{23}-, -C(=S)NR^{23}-, -C(=O)NR^{23}-CH_2-, -C(=S)NR^{23}-CH_2-, -C(=O)O-, -C(=S)O-, -C(=O)O-CH_2-, -C(=S)O-

CH_2-,

R^{23} can represent hydrogen or C_1-C_{10} alkyl, and

EG is a recognition unit of general formula (IV):



IV,

in which

R^{24} can represent a group CH_2OPG^4 or a group CO_2R^{26},

PG^1, PG^2, PG^3, and PG^4, independently of one another, can represent hydrogen or a protective group PG,

R^{26} can represent hydrogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_4-C_7 cycloalkyl, which can contain an oxygen atom, aryl, aralkyl, tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, or tris(aralkyl)-silyl,

as a uniform isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

2. Conjugate according to claim 1, whereby:

A-Y represents O-C(=O) or NR^{21}-C(=O),

D-E represents an H_2C-CH_2 group or an HC=CH group,

G represents a CH_2 group,

Z represents an oxygen atom,

R^{1a}, R^{1b} in each case represent C_1-C_{10} alkyl or together a $-(CH_2)_p$ group with

p equal to 2 or 3 or 4,

R^{2a}, R^{2b}, independently of one another, represent hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 represents hydrogen;

R^{4a}, R^{4b}, independently of one another, represent hydrogen or C_1-C_{10} alkyl;

R^5 represents hydrogen or C_1-C_4 alkyl or CH_2OH or CH_2NH_2 or $CH_2N(alkyl, acyl)_{1,2}$ or CH_2Hal,

R^6 and R^7 together represent an additional bond or together an NH group or together an N-alkyl group or together a CH_2 group or together an oxygen atom,

W represents a group $C(=X)R^8$ or a 2-methylbenzothiazol-5-yl radical or a 2-methylbenzoxazol-5-yl radical or a quinolin-7-yl radical or a 2-aminomethylbenzothiazol-5-yl radical or a 2-hydroxymethylbenzothiazol-5-yl radical or a 2-aminomethylbenzoxazol-5-yl radical or a 2-hydroxymethylbenzoxazol-5-yl radical,

X represents a $CR^{10}R^{11}$ group,

R^8 represents hydrogen or C_1-C_4 alkyl or a fluorine atom or a chlorine atom or a bromine atom,

R^{10}/R^{11} represent hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl or hydrogen/2-methyloxazol-4-yl or hydrogen/2-aminomethylthiazol-4-yl or hydrogen/2-aminomethyloxazol-4-yl or hydrogen/2-hydroxymethylthiazol-4-yl or hydrogen/2-hydroxymethyloxazol-4-yl.

3. Conjugate according to claim 1 or 2, whereby:

R^{22a}, R^{22b} represent C_1-C_8-alkyl, C_1-C_8-alkoxy, halogen, nitro, CN, N_3, NH_2, or CO_2-(C_1-C_8-alkyl).

4. Conjugate according to one of claims 1 to 3, whereby:

R^{26} represents C_1-C_8-alkyl or C_2-C_8-alkenyl.

5. Conjugate according to one of claims 1 to 4, whereby:

R^{2a} represents hydrogen and R^{2b} represents C_1-C_7-alkyl, C_2-C_7-alkenyl or C_2-C_7-alkinyl; or R^{2b} represents hydrogen and R^{2a} represents C_1-C_7-alkyl, C_2-C_7-alkenyl or C_2-C_7-alkinyl.

6. Conjugate according to one of claims 1 to 5, whereby:

R^{22a}, R^{22b} represent methyl, ethyl, propyl, i-propyl, *tert.*butyl, CF_3, C_2F_5, F, Cl, nitro, CN, N_3, NH_2, CO_2-methyl, CO_2-ethyl, CO_2-propyl or CO_2-i-propyl.

7. Conjugate according to one of claims 1 to 6, whereby:

R^{26} represents methyl, ethyl, propyl, i-propyl, t-butyl, CF_3, propenyl or butenyl.

8. Conjugate according to one of claims 1 to 7, whereby:

R^{2a} represents hydrogen, and R^{2b} represents methyl, ethyl, propyl, i-propyl,

propenyl, butenyl, propinyl or butinyl; or R^{2b} represents hydrogen, and R^{2a} represents methyl, ethyl, propyl, i-propyl, propenyl, butenyl, propinyl or butinyl.

9. Conjugate according to one of claims 1 to 8, whereby the effector element is selected from the group that consists of:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]-heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

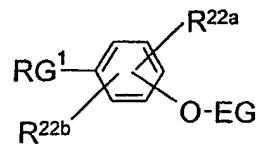
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

whereby the hydrogen atoms in the above-mentioned effector elements are replaced by radicals L^1-L^3 in the positions indicated in formula (I).

10. Conjugate according to one of claims 1 to 9, whereby the conjugate contains more than one recognition unit, and whereby the recognition units are identical.

11. A linker-recognition unit of general formula (III^1):



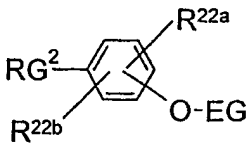
III^1,

in which

RG^1 represents an O=C=N group or an S=C=N group or an O=C=N-CH_2 group or an S=C=N-CH_2 group; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1;

or a linker-recognition unit of general formula (III^2):



III^2,

in which

RG^2 represents an HO-CH_2 group or an HNR^{23}-CH_2 group; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1;

but with the condition that the following compounds are not included:

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(2-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(4-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside;

(2-Hydroxymethyl-4-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

(4-Hydroxymethyl-2-nitro)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

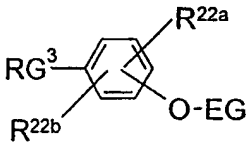
(2-Hydroxymethyl-4-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(4-Hydroxymethyl-2-nitro)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

(2-Chloro-4-hydroxymethyl)phenyl-2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside;

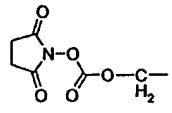
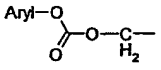
(2-Chloro-4-hydroxymethyl)phenyl-2,3,4-tri-O-acetyl-β-D-glucuronide-6-methyl ester;

or a linker-recognition unit of general formula (III^3):



III^3,

in which

RG^3 represents a Hal-C(=O)-CH_2 group or a Hal-C(=S)-CH_2 group or an R^{27}-C(=O)-O-C(=O)-CH_2 group or an R^{27}-C(=O)-O-C(=S)-CH_2 group or a  group or a  group;

R^{27} is C_1-C_{10} alkyl, aryl or aralkyl; and

R^{22a}, R^{22b} and EG have the meanings that are mentioned in claim 1;

but with the condition that the following compounds are not included:

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)-methyluronate)benzyl]carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-benzyl]carbonate;

2,5-Dioxopyrrolidin-1-yl-[4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-benzyl]carbonate;

4-Nitrophenyl-[2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-5-nitrobenzyl]carbonate;

4-Nitrophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate;

4-Nitrophenyl-[4-methoxy-5-nitro-2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)benzyl]carbonate;

4-Nitrophenyl-[4-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate;

4-Chlorophenyl-[2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronate)-5-nitrobenzyl]carbonate.

12. Process for the production of conjugates according to one of claims 1-10, whereby a compound of general formula (I), in which the substituents have the meanings that are mentioned in claim 1, but

the condition that at least one substituent L^1, L^2, or L^4 represents a linker-recognition unit of general formula (III) need not be met, and

at least one substituent L^1, L^2, or L^4 represents hydrogen, a group C(=O)Cl or a group C(=S)Cl,

is reacted with a linker-recognition unit, which is selected from the group that consists of a linker-recognition unit of general formula (III^1) or (III^2) or (III^3), as described in claim 11.

13. Use of a compound of general formula (I), whereby the substituents have the meanings that are mentioned in claim 1, but

the condition that at least one substituent L^1, L^2, or L^4 represents a linker-recognition unit of general formula (III) need not be met, and

at least one substituent L^1, L^2, or L^4 represents hydrogen, a group C(=O)Cl or a group C (+S)Cl;

in a process according to claim 12.

14. Use of a compound of general formula (I) for the production of a conjugate according to claims 1 to 10.

15. Use of a linker-recognition unit of general formula (III1), (III)2 or (III3) in a process according to claim 12.

16. Use of a linker-recognition unit of general formula (III1), (III2) or (III3) for the production of a conjugate according to one of claims 1 to 10.

17. Conjugate according to one of claims 1 to 10 for use as a medication.

18. Conjugate according to one of claims 1 to 10 for use as a medication for

treating diseases that are associated with proliferative processes.

19. Conjugate according to claim 18 for the use mentioned therein, whereby the disease is selected from the group that consists of tumor diseases, inflammatory diseases, neurodegenerative diseases, angiogenesis-associated diseases, multiple sclerosis, Alzheimer's disease and rheumatoid arthritis.

20. Conjugate according to one of claims 1 to 10 for treatment of primary tumors and/or metastases that are not operatively accessible.

21. Conjugate according to claim 20 for the use mentioned therein, whereby the conjugate is administered in combination with one or more substances to trigger enhanced cell death (apoptosis) and necrosis.

22. Conjugate according to claim 20 for the use mentioned therein, whereby the conjugate is administered in combination with one or more substances that is/are selected from the group that consists of an L19 construct, EDB-fibronectin and a combrestatin A4 prodrug.

INTERNATIONAL SEARCH REPORT

Int ial Application No
PCT/EP 03/13780

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/427 C07D417/14 C07D493/04 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/012735 A (SCHERING AG) 12 February 2004 (2004-02-12) claims 1-28	1-10, 12-22
Y	BOSSLET ET AL: "Elucidation of the mechanism enabling tumor selective prodrug monotherapy" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, 15 March 1998 (1998-03-15), pages 1195-1201, XP002108804 ISSN: 0008-5472 cited in the application the whole document	1-10, 12-22
Y	EP 0 648 503 A (BEHRINGWERKE AG ;HOECHST SA LAB (FR)) 19 April 1995 (1995-04-19) claim 4	1-10, 12-22

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2004	17/05/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bérillon, L

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Int — nal Application No
PCT/EP 03/13780

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 647 450 A (BEHRINGWERKE AG) 12 April 1995 (1995-04-12) claim 1	1-10, 12-22
Y	EP 0 595 133 A (BEHRINGWERKE AG ;HOECHST SA LAB (FR)) 4 May 1994 (1994-05-04) claim 1	1-10, 12-22
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 7717244 XP002278521 abstract	11
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 52924 XP002278522 abstract	11
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 1276877 XP002278523 abstract	11
A	NICOLAOU K C ET AL: "Chemical Biology of Epothilones" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 15, August 1998 (1998-08), pages 2014-2045, XP002131418 ISSN: 0570-0833 the whole document	

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 03/13780

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 11

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claim 11 (a few examples have been cited). So many documents were retrieved that it is impossible to determine which parts of claim 11 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of claim 11 is impossible. Consequently, the search has been restricted to claims 1-10, 12-22.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

In ıal Application No
PCT/EP 03/13780

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 04012735 5 A	19-04-2001	DE 19949549 A1	26-04-2001
		AU 7918900 A	23-04-2001
		BR 0014757 A	02-07-2002
		CA 2389376 A1	19-04-2001
		CN 1378607 T	06-11-2002
		WO 0127355 A1	19-04-2001
		EP 1240365 A1	18-09-2002
		JP 2003511563 T	25-03-2003
		PL 354574 A1	26-01-2004
EP 0648503 A	19-04-1995	EP 0648503 A1	19-04-1995
		GR 3034412 T3	29-12-2000
		AT 194920 T	15-08-2000
		AU 681180 B2	21-08-1997
		AU 7410994 A	06-04-1995
		CA 2132608 A1	23-03-1995
		DE 69425356 D1	31-08-2000
		DE 69425356 T2	18-04-2002
		DK 648503 T3	02-10-2000
		ES 2148259 T3	16-10-2000
		JP 7149666 A	13-06-1995
		NZ 264487 A	23-12-1998
		PT 648503 T	30-11-2000
		US 5877158 A	02-03-1999
		ZA 9407332 A	10-05-1995
EP 0647450 A	12-04-1995	EP 0647450 A1	12-04-1995
		AT 208213 T	15-11-2001
		AU 678494 B2	29-05-1997
		AU 7169994 A	23-03-1995
		CA 2131662 A1	10-03-1995
		DE 69428957 D1	13-12-2001
		DE 69428957 T2	06-06-2002
		DK 642799 T3	25-02-2002
		EP 0642799 A1	15-03-1995
		ES 2167343 T3	16-05-2002
		JP 7149667 A	13-06-1995
		NO 943319 A	10-03-1995
		PT 642799 T	29-04-2002
		US 5621002 A	15-04-1997
		ZA 9406920 A	12-04-1995
EP 0595133 A	04-05-1994	DE 4236237 A1	28-04-1994
		AU 669218 B2	30-05-1996
		AU 5022593 A	12-05-1994
		CA 2109259 A1	28-04-1994
		EP 0595133 A2	04-05-1994
		IL 107398 A	28-01-2001
		JP 6293665 A	21-10-1994
		NO 933854 A	28-04-1994
		NZ 250030 A	22-12-1994
		US 5955100 A	21-09-1999
		US 6146658 A	14-11-2000
		ZA 9307951 A	05-07-1995